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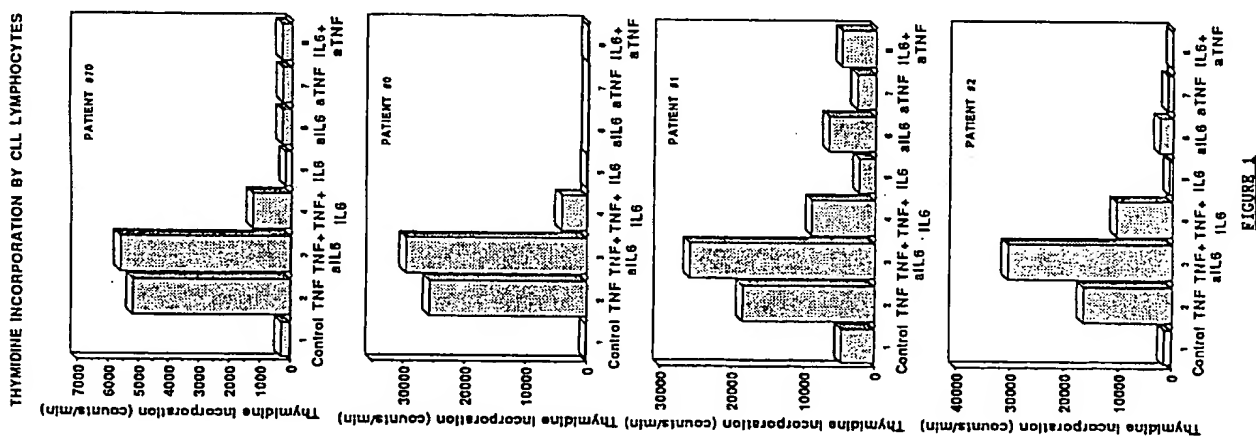
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⑤ Int. Cl.⁵: **A61K 37/02**

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⑤7 IL-6 is useful in the treatment of chronic lymphocytic leukemia (CLL) and B-cell lymphomas.



Field of the Invention

The present invention relates to the use of interleukin-6 and/or salts, functional derivatives, muteins or active fractions thereof, for the manufacture of a pharmaceutical composition for the treatment of chronic lymphocytic leukemia and B-cell lymphomas. The invention further relates to such use together with the soluble interleukin-6 receptor and to pharmaceutical compositions.

Background of the Invention

B-cell neoplasms are a heterogeneous group of diseases characterized by different maturation states of the B-cell, which are related to the aggressiveness of the disorder. Accordingly, the lymphomas are classified into three groups: low grade, intermediate grade and high grade lymphomas. The "low grade" nodular lymphocytic, well-differentiated lymphoma is occasionally confused with chronic lymphocytic leukemia because of the identical histologic picture.

Chronic lymphocytic leukemia (CLL) is characterized by proliferation and accumulation of B-lymphocytes that appear morphologically mature but are biologically immature. CLL typically occurs in persons over 50 years of age. This disorder accounts for 30% of leukemias in Western countries, with 10,000 new cases being diagnosed annually in the United States alone⁽¹⁾.

The disorder is characterized by proliferation of biologically immature lymphocytes, unable to produce immunoglobulins, which upon organ infiltration cause lymph-node enlargement and hepato-splenomegaly. In the advanced stages of the disease, bone marrow occupation by the abnormal lymphocytes results in bone marrow failure, resulting in anemia and thrombocytopenia.

The B-cells in CLL have receptors for mouse erythrocytes, a marker of immature B-cells. An increased number of T-cells has been reported in this disorder with an increase in the number of T-suppressor cells⁽²⁻⁵⁾. Some data support the possibility that B-CLL cells secrete an inhibitory factor that suppresses T-cell function⁽⁶⁾. In addition, in 50% of CLL patients, chromosome abnormalities were detected and recent evidence suggests that chromosomal analysis provides prognostic information about overall survival, in addition to that supplied by clinical data in patients with B-cell CLL⁽⁷⁾.

Several cytokines were reported to stimulate the growth of B-cells in general, such as interleukin-1⁽⁸⁾ and interleukin-6⁽⁹⁻¹¹⁾ (hereinafter IL-6), while tumor necrosis factor (TNF) was shown to serve as an autocrine tumor growth factor for the pathological B-cells in CLL^(12,13).

IL-6 was found to serve also as a growth stimulatory factor for certain B-cell neoplasms such as plasmacytoma, myeloma cells and derived hybridomas⁽⁹⁻¹¹⁾ or for Epstein-Barr virus (EBV)-transformed B lymphocytes⁽¹⁷⁾. In B-cell CLL, constitutive expression of the IL-6 gene was found, but the biological significance of IL-6 expression in B-CLL was not fully elucidated⁽¹⁴⁾.

As mentioned above, TNF was shown to serve as an autocrine tumor growth factor for B-cell CLL^(12,13), prolonging the survival of B-cell CLL cells and inducing them to proliferate⁽¹⁵⁾.

mRNA for IL-6 is induced by TNF in B-CLL cells; this cytokine could then be the agent responsible for the proliferative events of the leukemic cells. If B-cell CLL is dependent on autocrine growth factors for survival, interruption of the autocrine loop would be of therapeutic value⁽¹⁵⁾. Such interruption of the autocrine growth-stimulating loop was obtained with interferon- α ⁽¹⁶⁾, yet administration of this cytokine to CLL-patients was not beneficial.

IL-6 does not promote the growth of normal B-lymphocytes. Since the growth effect of IL-6 is seen in EBV transformed cells or in B-cell tumors, it was anticipated that the growth of leukemic B-cells from CLL patients will be also stimulated by this cytokine.

However, contrary to expectations, the present invention shows that the TNF induced proliferation of the leukemic lymphocytes from CLL patients (as measured by ³H-thymidine incorporation) is inhibited by IL-6.

Summary of the Invention

We have now found in accordance with the present invention that IL-6 inhibits TNF- α and TNF- β - (hereinafter both will be designated "TNF") induced proliferation of leukemic lymphocytes from CLL patients.

The present invention thus relates to the use of IL-6 and/or salts, functional derivatives, muteins or active fractions thereof, in the manufacture of a pharmaceutical composition for the treatment of CLL or B-cell lymphomas.

In another aspect, the invention relates to the use of IL-6 and/or salts, functional derivatives, muteins or active fractions thereof, together with the soluble IL-6 receptor, in the manufacture of a pharmaceutical

composition for the treatment of CLL or B-cell lymphomas.

In yet another aspect, the invention relates to pharmaceutical compositions for the treatment of CLL or B-cell lymphomas, comprising IL-6 and/or salts, functional derivatives, muteins or active fractions thereof, as active ingredient, optionally together with pharmaceutically acceptable carriers and/or excipients and/or adjuvants and comprising the soluble IL-6 receptor as a further active ingredient.

Detailed Description of the Invention

It was found in accordance with the present invention that the TNF-induced proliferation of leukemic lymphocytes from CLL patients (as determined by ³H-thymidine incorporation) is inhibited by IL-6. This IL-6 inhibition of TNF effects is even more pronounced in the presence of its soluble receptor (sIL-6 R), known to assist IL-6 in its biological activity⁽¹⁸⁾.

The inhibition of leukemic lymphocytes by IL-6 was demonstrated in a sub-group of CLL patients whose lymphocytes proliferate in the presence of TNF. The IL-6 induced inhibition of B-CLL lymphocytes is observed with autologous TNF as well as with its exogenous addition to cultures.

The invention shows that the autologous IL-6 production by the cells is important to overcome the proliferative signals of TNF, but is probably insufficient to completely abolish these effects.

The IL-6 inhibition of the TNF growth stimulatory effects is further supported by two additional observations: (a) Neutralization of IL-6 by anti-IL-6 Ab, resulted in augmentation of the B-cell CLL lymphocyte proliferation in response to TNF; and (b) Prevention of IL-6 action by neutralization of its cell-associated receptor with anti-IL-6 Receptor Ab, resulted in a sharp increase in the proliferation of the leukemic lymphocytes as determined by ³H-thymidine incorporation.

The inhibition by IL-6 of TNF-induced growth and proliferation B-cell CLL lymphocytes can be exploited clinically to arrest and possibly to induce remission in CLL.

IL-6 can also increase the number of thrombocytes in this disease and augment immunoglobulin production, which are impaired in this disorder.

As used herein the term 'salts' refers to both salts of carboxyl groups and to acid addition salts of amino groups of the protein molecule. Salts of a carboxyl group may be formed by means known in the art and include inorganic salts, for example, sodium, calcium, ammonium, ferric or zinc salts, and the like, and salts with organic bases as those formed, for example, with amines, such as triethanolamine, arginine or lysine, piperidine, procaine and the like. Acid addition salts include, for example, salts with mineral acids such as, for example, hydrochloric acid or sulfuric acid, and salts with organic acids such as, for example, acetic acid or oxalic acid.

"Functional derivatives" as used herein covers derivatives which may be prepared from the functional groups which occur as side chains on the residues or the N- or C- terminal groups, by means known in the art, and are included in the invention as long as they remain pharmaceutically acceptable, i.e. they do not destroy the activity of the protein and do not confer toxic properties on compositions containing it.

These derivatives may, for example, include aliphatic esters of the carboxyl groups, amides of the carboxyl groups by reaction with ammonia or with primary or secondary amines, N-acyl derivatives of free amino groups of the amino acid residues formed with acyl moieties (e.g. alkanoyl or carbocyclic aroyl groups) or O-acyl derivatives of free hydroxyl group (for example that of seryl or threonyl residues) formed with acyl moieties.

As "active fractions" of the IL-6, the present invention covers any fragment or precursors of the polypeptide chain of the protein molecule alone or together with associated molecules or residues linked thereto, e.g. sugar or phosphate residues, or aggregates of the protein molecule or the sugar residues by themselves, provided said fraction has the same biological activity as IL-6 and remains pharmaceutically acceptable.

"Muteins" are those proteins in which one or more amino acids of the IL-6 amino acid sequence are replaced with another amino acid or are deleted altogether, provided that the resulting mutein exhibits the same biological activity as IL-6 and is pharmaceutically acceptable.

The pharmaceutical compositions according to the invention are administered via the accepted ways of administration. Preferred ways of administration are intravenous, intramuscular or subcutaneous. The pharmaceutical compositions may also be administered continuously, i.e. by way of infusion. The formulation and dose will depend on the condition to be treated, the route of administration and the condition and the body weight of the patient to be treated. The exact dose will be determined by the attending physician.

The pharmaceutical compositions according to the invention are prepared in the usual manner, for example by mixing the active ingredient with pharmaceutically and physiologically acceptable carriers and/or stabilizers and/or excipients, as the case may be, and are prepared in dosage form, e.g. by

lyophilization in dosage vials.

Brief Description of the Figures

- 5 Fig. 1 shows the ^3H -thymidine incorporation by CLL lymphocytes of 4 different patients in response to TNF, TNF and IL-6, TNF and anti-IL-6 antibodies, and the respective controls.
- Fig. 2 shows reduction in ^3H -thymidine incorporation in B-CLL cells treated with IL-6, compared to control cells (without exogenous TNF).
- 10 Fig. 3 shows that the effects of IL-6 from different sources exert similar influences on B-cell CLL cells.
- Fig. 4a shows the ^3H -thymidine incorporation into B-CLL lymphocytes of 3 different patients as a function of lymphotoxin (TNF- β) concentration.
- Fig. 4b shows the inhibitory effect of IL-6 on both TNF and lymphotoxin-induced growth of the leukemic B-cells.
- 15 Fig. 5 shows the ^3H -thymidine incorporation by CLL lymphocytes of two different patients and the influence of the sIL-6-R on the IL-6 induced inhibition of the proliferation of the leukemic cells in response to TNF. These responses are compared to those of healthy controls.
- Fig. 6 shows photographs of the leukemic cells grown in the presence of IL-6, TNF, IL-6-R, anti IL-6 antibodies, and their different combinations.
- 20 Fig. 7 shows the effects of TNF, IL-6, anti-IL-6 Ab, IL-6-R and their different combinations on 4 different cell populations: B-cells, B-cells + T-cells, B-cells + monocytes, and a combination of all three.

The following examples illustrate the invention without limiting it thereto:

25 EXAMPLE 1: IL-6 inhibits TNF induced proliferation of leukemic B-CLL cells

Mononuclear leukocytes of B-chronic lymphocytic leukemia (B-CLL) patients were isolated from the peripheral blood by centrifugation on a Ficoll-Hypaque cushion (Pharmacia, Uppsala, Sweden). To enrich the leukocyte fraction of leukemic cells, the mononuclear leukocytes were depleted of T-cells by rosetting with sheep erythrocytes⁽¹⁹⁾, and then further depleted of the mononuclear phagocytes by adherence to plastic⁽²⁰⁾. The leukocytes were cultured in RPMI 1640 medium, supplemented with 10% fetal calf serum.

B-CLL cells were cultured in 96-well microtiter plates at densities of 2.5×10^5 cells/0.2 ml/well and 5×10^3 cells/0.2 ml/well respectively. The rate of cell growth following the indicated culture time was assessed by measuring the incorporation of ^3H -thymidine into the DNA of the cells. Labelled thymidine (25Ci/mmol. Amersham, UK) was applied to the cultures (1 μCi /well) for the last 8 hrs. of incubation and the amount of radioactivity incorporated into DNA was then determined after harvesting the cells with the aid of a PHD cell harvester (Cambridge Technology Inc., Watertown, MA). The cells were lysed by washing with distilled water and the label bound to the filter was measured by liquid scintillation counting.

As shown in Fig. 1, TNF (20 ng/ml) enhanced significantly the ^3H -thymidine incorporation of B-cells (lane 2) compared to control (lane 1). Addition of monoclonal anti-IL-6 antibodies (1:400), resulted in augmentation of the growth stimulation by TNF (lane 3). Addition of IL-6 (12.5 ng/ml) blunted the growth stimulation induced by TNF, by 35-85%. This observation suggests that IL-6 inhibits the TNF stimulatory effect on B-CLL cells. This effect was seen in additional 5 consecutive patients examined. IL-6 alone, without exogenous addition of TNF would reduce the ^3H -thymidine incorporation into B-CLL cells by 12-65%, only in those patients whose leukemic lymphocytes were TNF responsive (Fig. 2).

These results imply that the effects of IL-6 on leukemic B-CLL cells are TNF linked.

The above data are the first to demonstrate direct antagonism of IL-6 to a TNF function; antagonism of IL-6 to TNF production was previously demonstrated by us ⁽²¹⁾ and others ⁽²²⁾.

50 EXAMPLE 2: The IL-6 inhibitory effect is not linked to a specific IL-6 batch

B-CLL leukemic lymphocytes were separated from one donor (# 200), as described in example 1. The cells were incubated in the presence of different recombinant IL-6 batches.

- a. A recombinant CHO IL-6 batch, designated batch 1/4
- 55 b. A recombinant CHO IL-6 batch, designated batch 1/17
- c. A recombinant E. coli IL-6 batch.

Using identical concentrations of each IL-6 preparation (about 60 u/ml), significant antagonism to the growth stimulatory effect of TNF was obtained with each preparation (Fig. 3): 70% with the recombinant

CHO 1/4 batch, 58% with the recombinant CHO 1/17 batch and 67% with the recombinant E. coli batch. This suggested that the inhibitory capacity was not restricted to a specific IL-6 batch or related to a non-specific toxic effect related to some contaminant impurities.

5 EXAMPLE 3: IL-6 inhibits the growth stimulatory effects of lymphotoxin

B-CLL cells were separated as described in example 1, and then grown in 96-well plates for 7 days in the presence of lymphotoxin (TNF- β) in increasing concentrations (Fig. 4a). The ^3H -thymidine incorporation increased dramatically as a function of the lymphotoxin concentration.

10 When the leukemic cells were grown in the presence of lymphotoxin and IL-6 (about 50 u/ml), the ^3H -thymidine incorporation was significantly reduced as shown in Fig. 4b. This demonstrates the ability of IL-6 to antagonize both the TNF- α and TNF- β growth stimulatory effects on B-CLL cells.

EXAMPLE 4: Soluble IL-6 receptor supports the IL-6 inhibition of TNF effects in B-CLL cells

15 Additional support to the inhibitory effect of IL-6 on the growth stimulatory effects of TNF on B-CLL leukemic cells was obtained from the incubation of the cells with IL-6 and its soluble receptor (sIL-6R) (Fig. 5).

20 As previously reported, IL-6 combines with its soluble receptor and the complex binds to an additional cell surface receptor designated gp 130 (18). This results in transduction of the IL-6 signal into the cell, with augmentation of its effect.

As shown in Fig. 5, IL-6 alone (12.5 ng/ml) reduced the TNF growth stimulatory effects (lane 4) by 34% (donor # 96) and 37% (donor # 97). The addition of the soluble IL-6 receptor (80 ng/ml) to IL-6 (lane 6) further reduced TNF effects by 65% and 61% respectively.

25 This observation is an additional support to the antagonism of IL-6 to the growth stimulatory effects of TNF on B-CLL cells.

EXAMPLE 5: IL-6 inhibits the multiplication of B-CLL cells in response to TNF

30 B-CLL cells were separated as described in example 1 and grown in the presence of TNF, IL-6, soluble IL-6 receptor and their different combinations (Fig. 6). IL-6 inhibited significantly the number of cells when grown in the presence of TNF. sIL-6-R aided IL-6 to further antagonize the TNF growth stimulatory effects.

35 EXAMPLE 6: The antagonism of IL-6 to TNF effects persist if B-CLL cells are combined with normal white blood cell elements

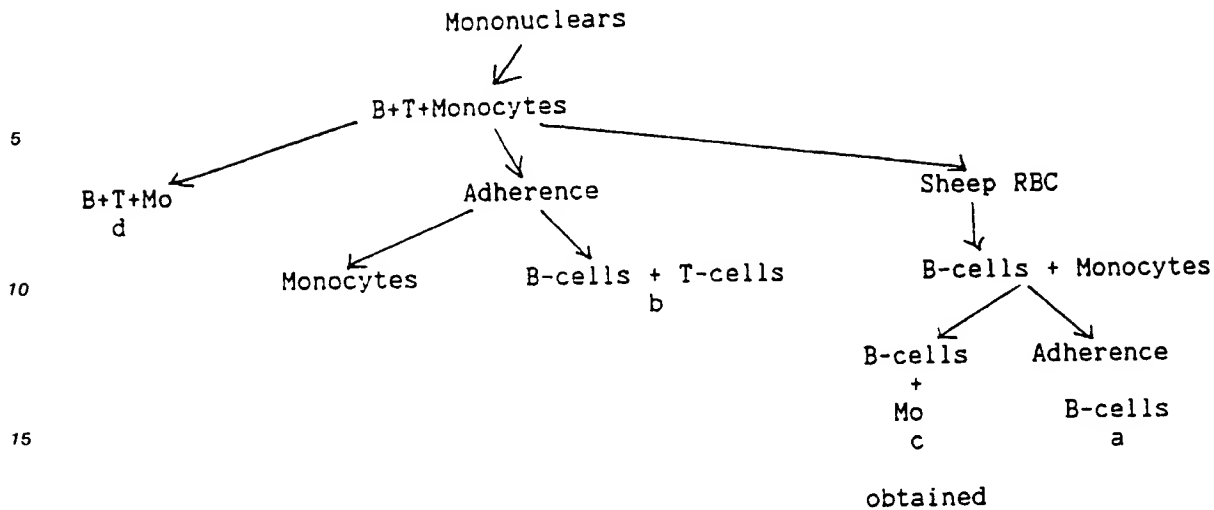
Further support to the antagonism of IL-6 to the stimulation of TNF to leukemic B-CLL cells is presented in Fig. 7.

40 Mononuclears were separated by Ficoll-Hypaque as described in example 1. Those mononuclears contained B-cells (leukemic), T-cells and monocytes. Part of this cell mixture was subjected to plastic adherence to eliminate monocytes and obtain a mixture of B- and T-cells, and part was incubated with sheep RBC to eliminate T-cells and thus to obtain a mixture of B-cells and monocytes. A part of this mixture was further subjected to plastic adherence in order to eliminate monocytes and obtain pure B-cells (see scheme).

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The 4 different populations obtained (a-d in above scheme) were further incubated in 96-well plates at a cell concentration of 300 000 cells/well, and the respective combinations of cytokines, soluble receptors or antibodies were added (see fig. 7).

In mixed cultures of B-cells + MØ or B-cells, T-cells and monocytes, addition of IL-6 antibodies (polyclonal) to TNF (lane 3) significantly augmented incorporation compared to TNF alone. This suggests autologous IL-6 production by the cells. Addition of polyclonal anti-IL-6-R antibodies (lane 7) augmented TNF's growth stimulatory effects preventing the inhibitory effects of autologous IL-6 production.

In mixed cultures of B-cells, T-cells and monocytes or B-cells + T-cells, anti-IL-6 antibodies (lane 8) or anti-IL-6 receptor antibodies (lane 10), significantly augmented the ³H-thymidine incorporation compared to control cells. Since the antagonism of autologous IL-6 (Table 1) was prevented by antibodies to the cytokine or its receptor, the cells proliferated in response to TNF produced spontaneously by these cultures (Table 2). This was determined by a cytotoxic assay as previously reported (23).

TABLE 1

Spontaneous IL-6 release by mononuclears (ng/ml) at 48° h					
Cell combinations	BTM	BT	BM	B	M
Healthy donor 1	15.1	4.32	-	3.75	15.5
Healthy donor 2	11.1	3.14	26.1	3.19	12.3
Patient 202 (CLL)	3.12	0	3.4	0	3.81
Patient 203 (CLL)	1.0	0	0	0	2.8
Patient 204 (CLL)	2.95	0.54	4.2	0	3.33

TABLE 2

Spontaneous TNF release by mononuclears (pcg/ml) at 48° h					
Cell combinations	BTM	BT	BM	B	M
Healthy donor 1	70	195	402	116	100
Healthy donor 2	80	45	230	70	28
Patient 202 (CLL)	25	20	35	15	35
Patient 203 (CLL)	0	10	28	4	45
Patient 204 (CLL)	35	46	65	0	132

B = B-cells

T = T-cells

M = Monocytes

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Claims

- 15 1. The use of interleukin-6 (IL-6), a salt, a functional derivative, a mutein or an active fraction thereof, or combinations of the foregoing, for the manufacture of a pharmaceutical composition for the treatment of chronic lymphocytic leukemia (CLL) and B-cell lymphomas.
2. Use according to claim 1, for treatment of CLL.
- 20 3. Use according to claim 1 or 2, wherein the composition also comprises the soluble IL-6 receptor.
4. The use according to any one of claims 1 to 3, wherein recombinant IL-6 is employed.

THYMIDINE INCORPORATION BY CLL LYMPHOCYTES

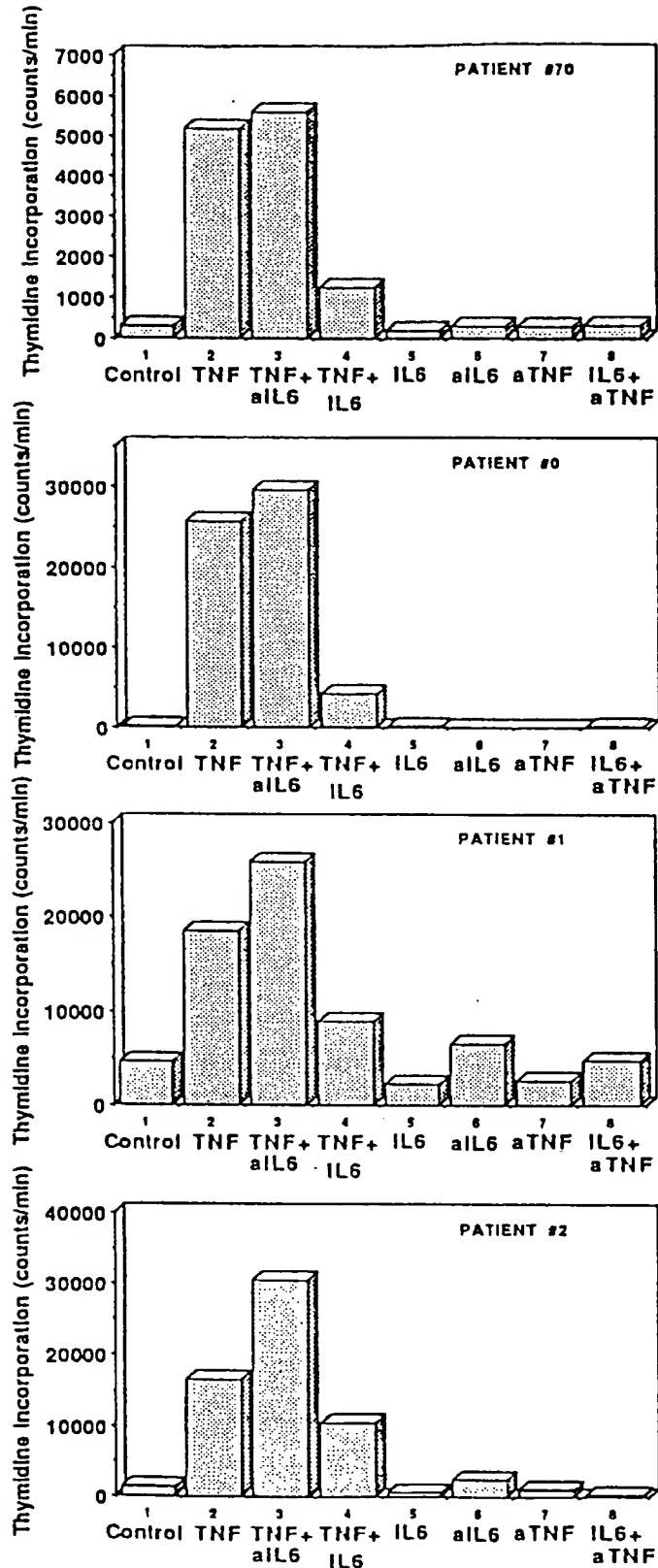


FIGURE 1

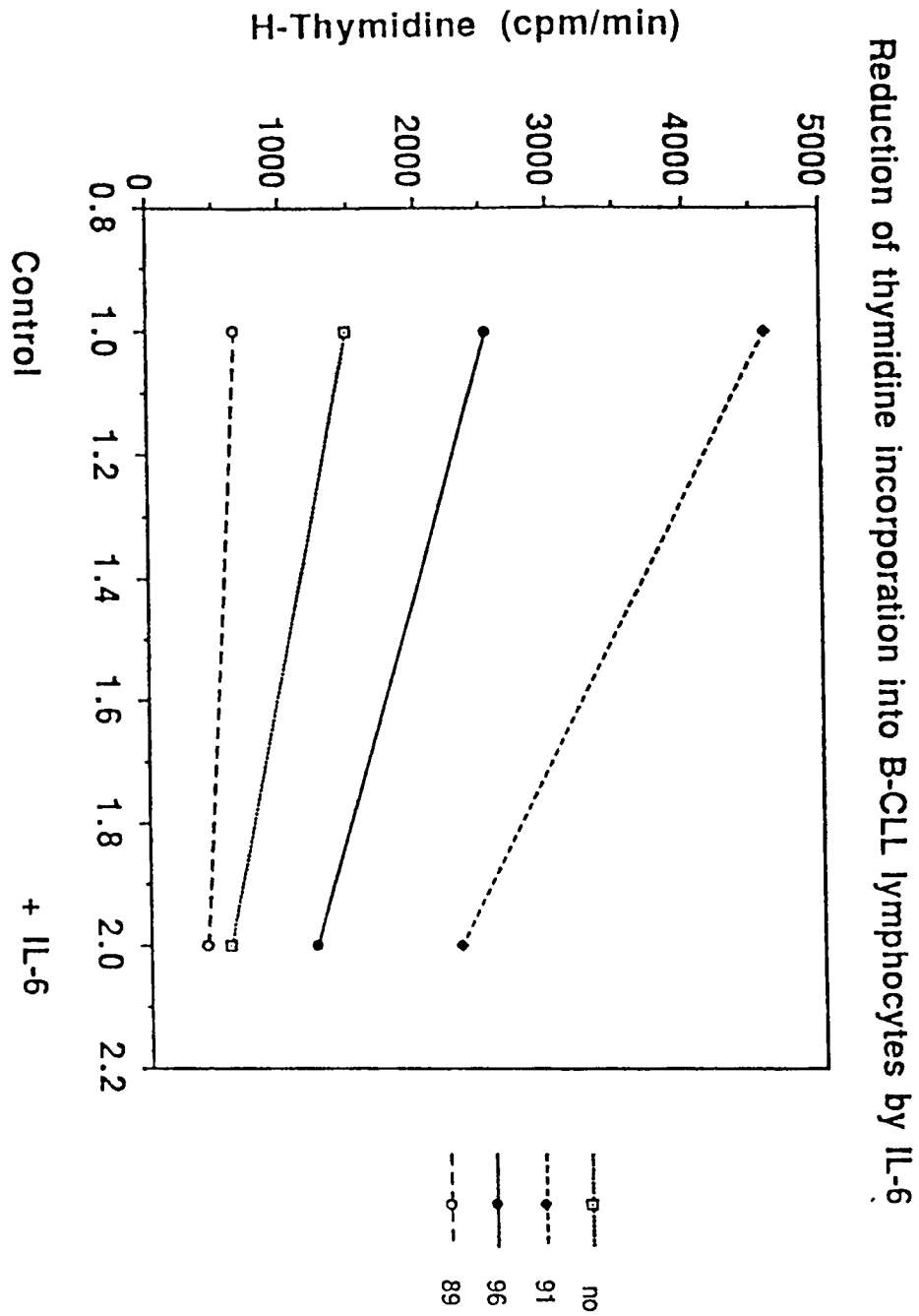


FIGURE 2

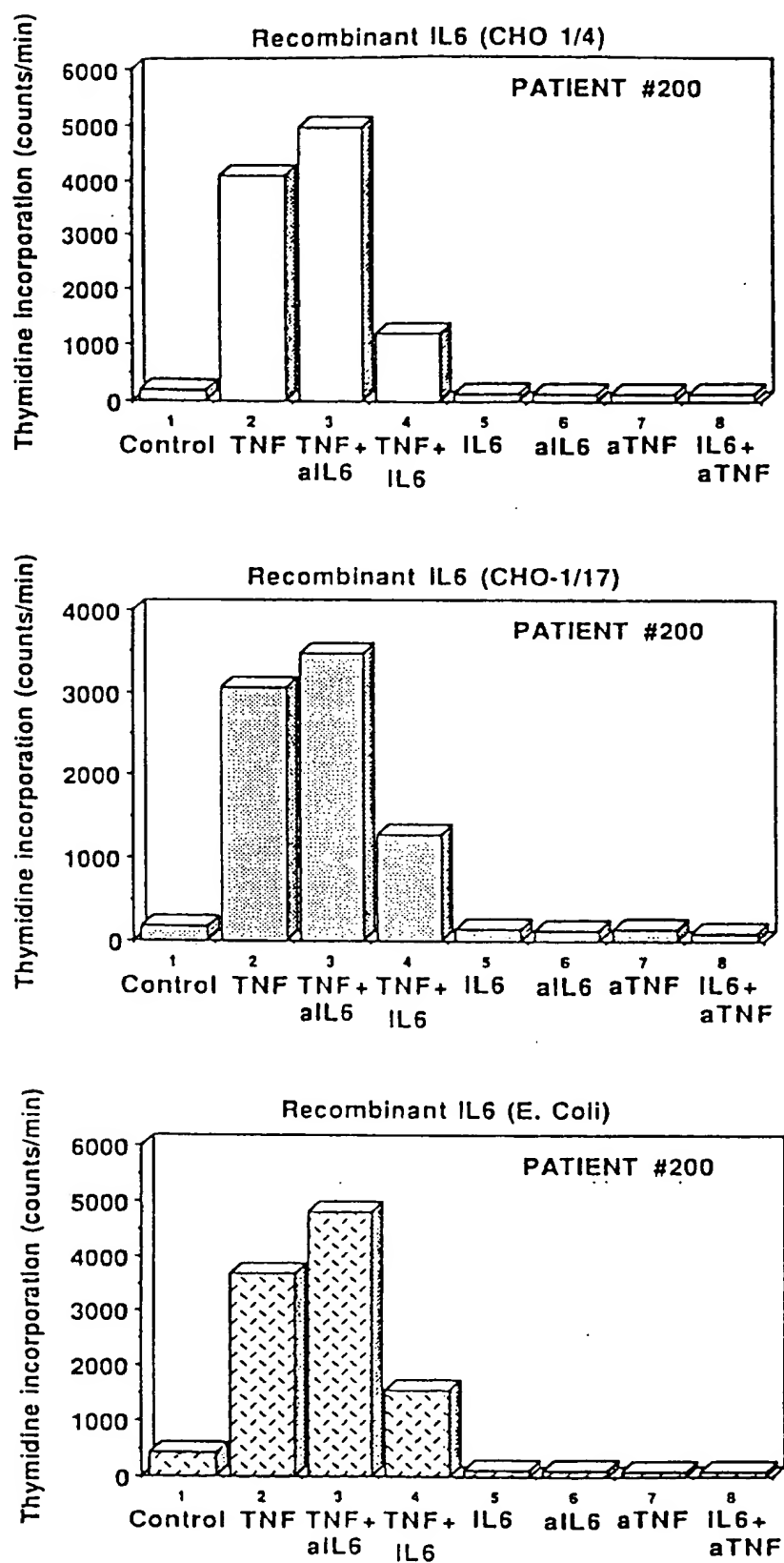


FIGURE 3

H-Thymidine Incorporation as a function of lymphotoxin concentration

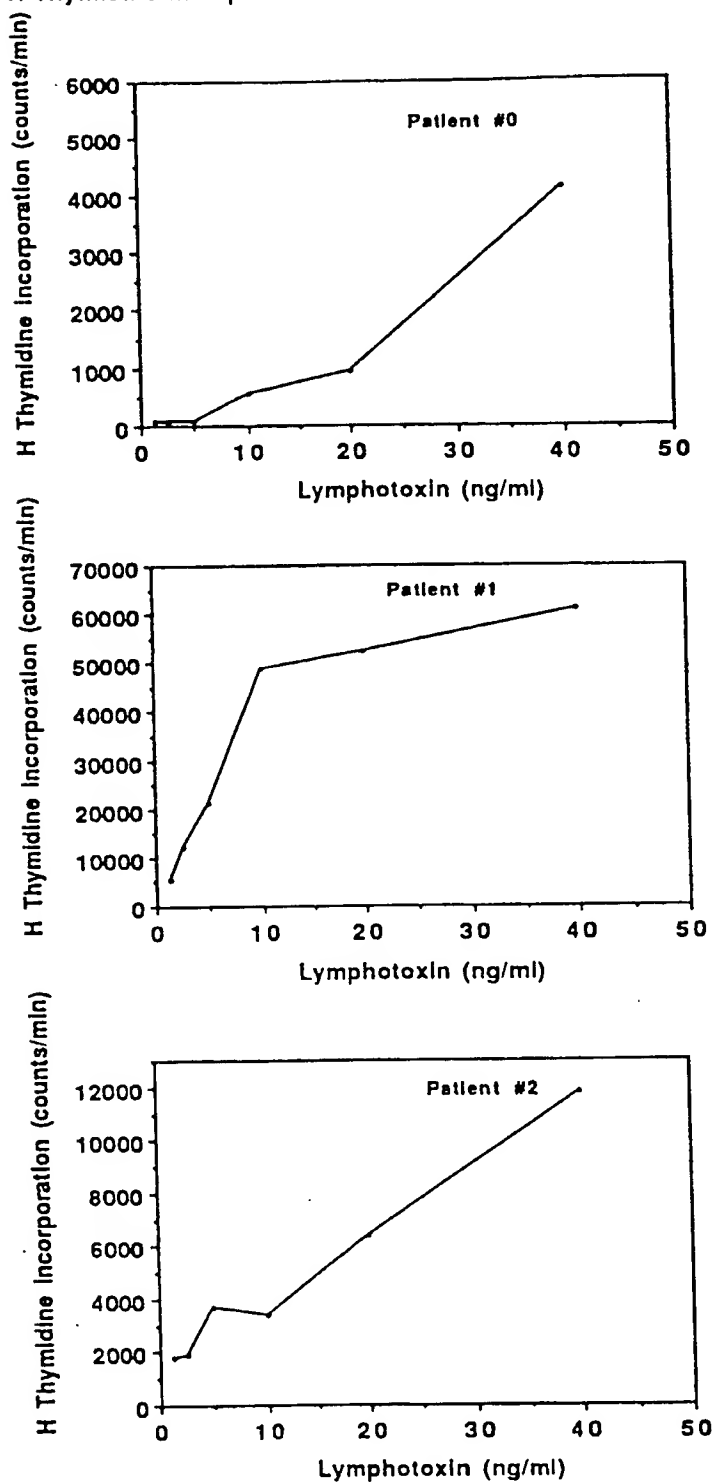


FIGURE 4a

Influence of IL-6 on the effects of TNF and Lymphotoxin on CLL lymphocytes

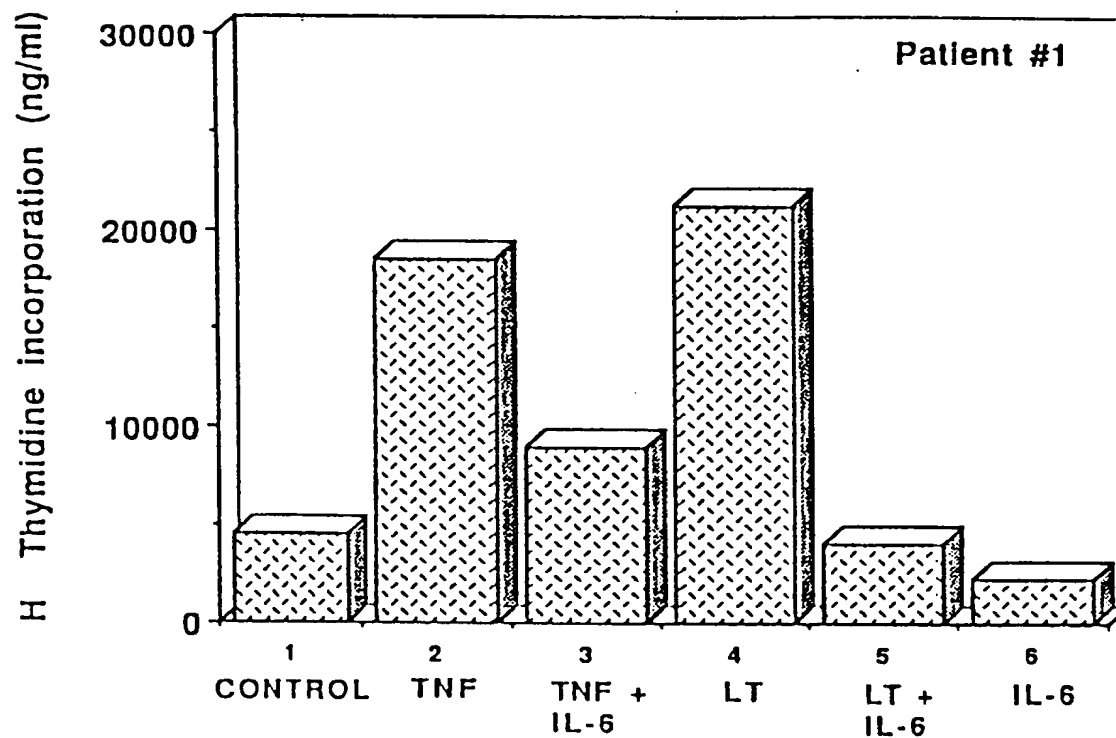


FIGURE 4b

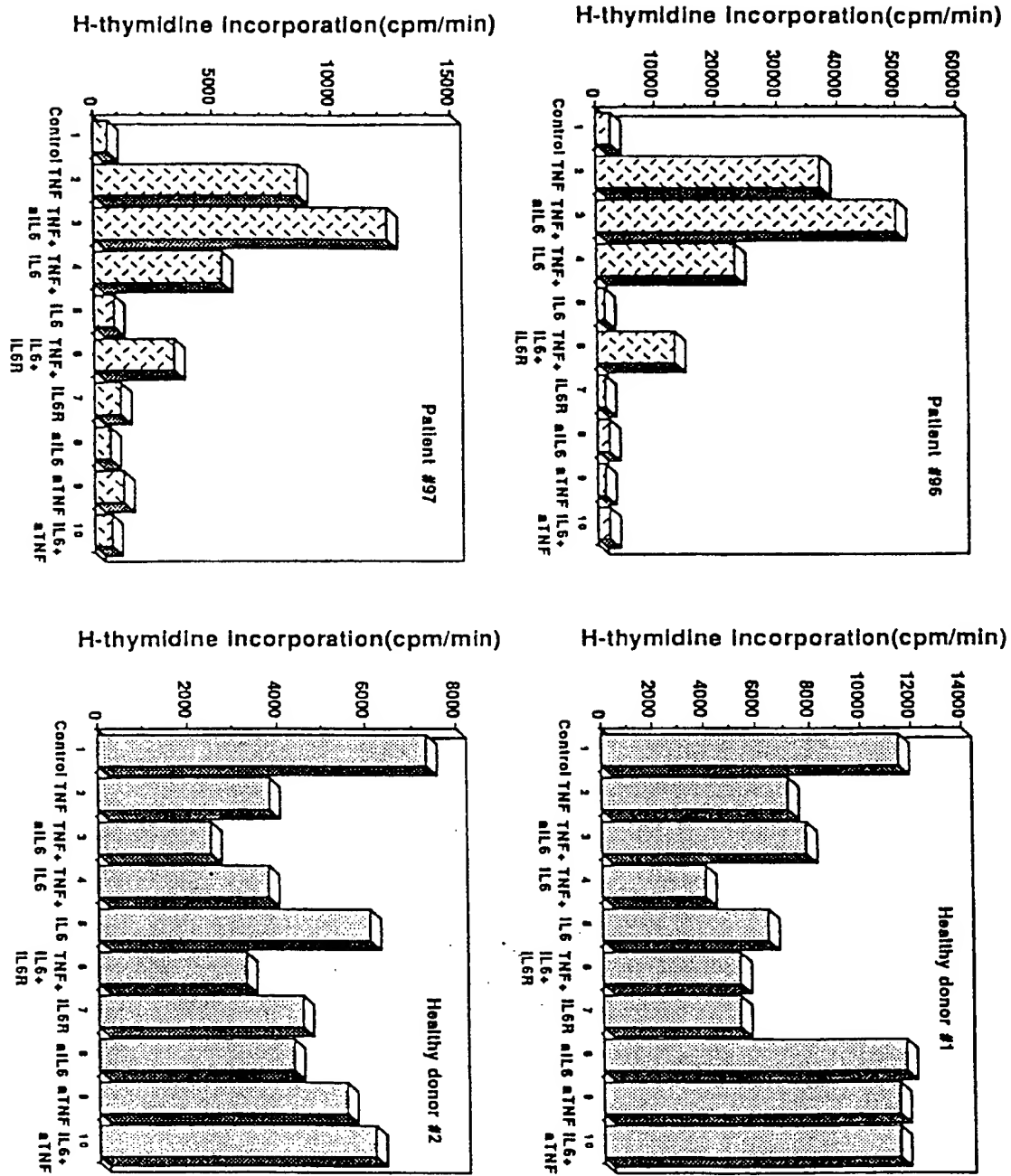


FIGURE 5

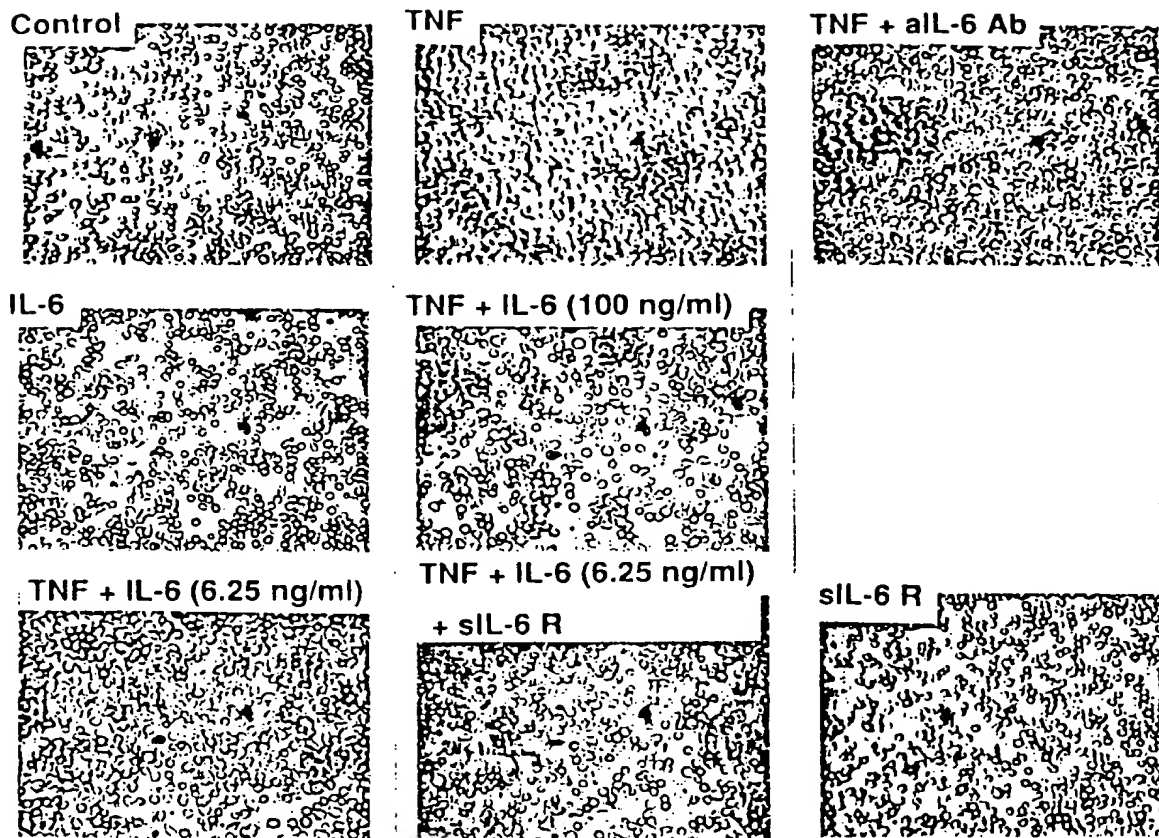


FIGURE 6

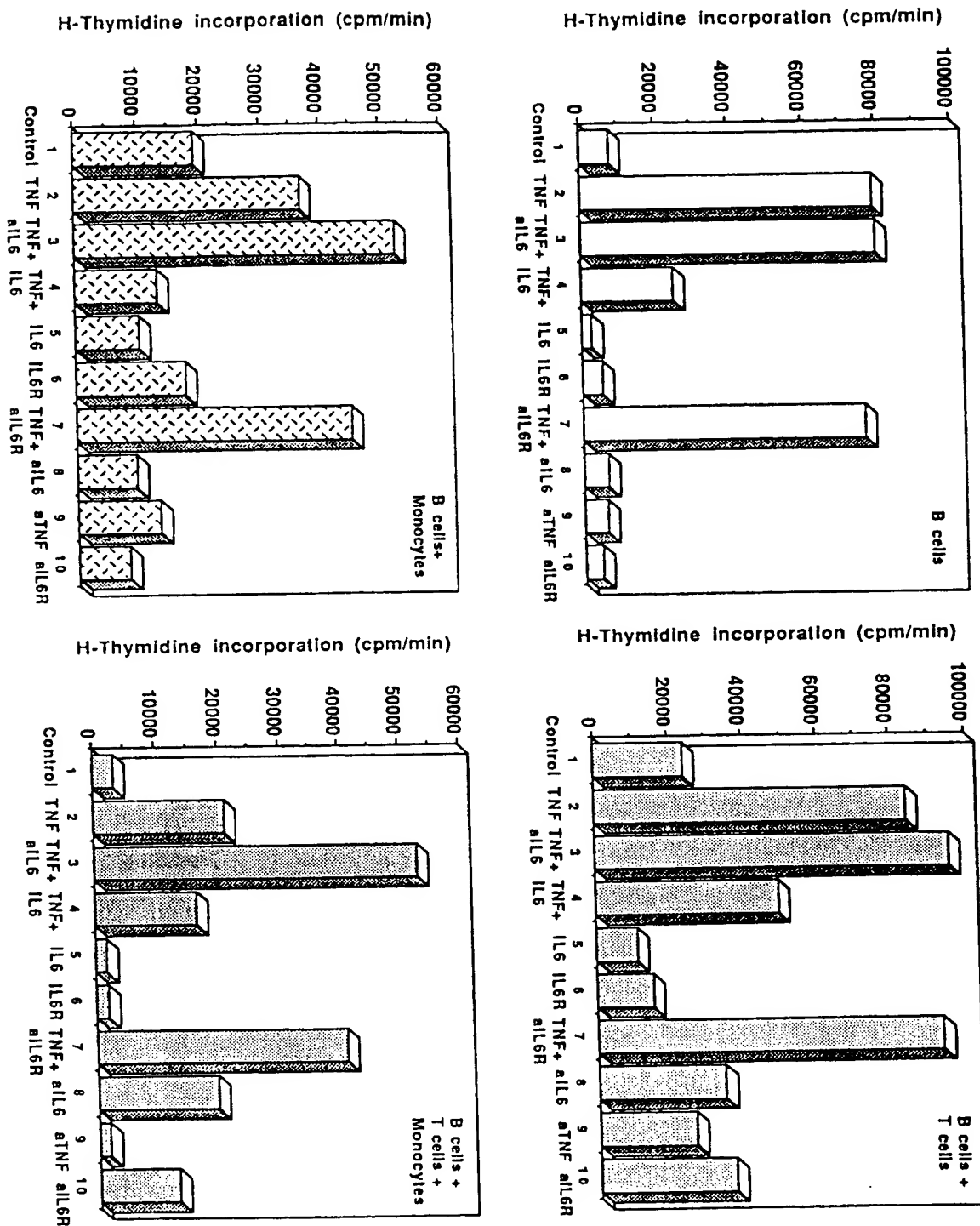


FIGURE 7



EUROPEAN PATENT APPLICATION

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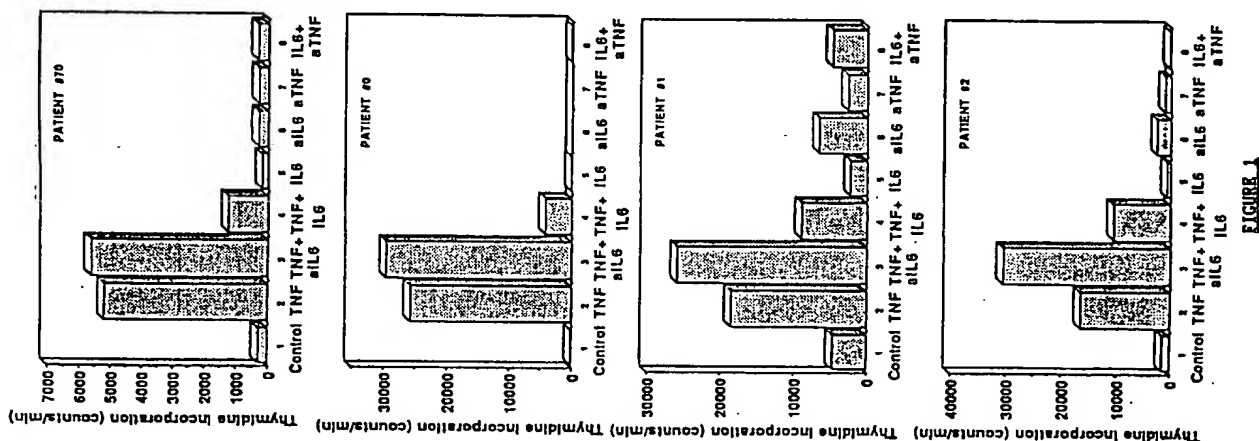
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54 **Pharmaceutical compositions comprising IL-6.**

⑤7 IL-6 is useful in the treatment of chronic lymphocytic leukemia (CLL) and B-cell lymphomas.





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EUROPEAN SEARCH REPORT

Application Number

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Page 1

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
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D,Y	JOURNAL OF IMMUNOLOGY. vol. 143, no. 11, 1 December 1989, BALTIMORE US pages 3517 - 3523 D. ADERKA ET AL. 'IL-6 INHIBITS LIPOPOLYSACCHARIDE-INDUCED TUMOR NECROSIS FACTOR PRODUCTION IN CULTURED HUMAN MONOCYTES, U937 CELLS, AND IN MICE.' * the whole document * ---	1,2,4	
D,Y	CELL. vol. 58, no. 3, 11 August 1989, CAMBRIDGE, MA, US pages 573 - 581 T. TAGA ET AL. 'INTERLEUKIN-6 TRIGGERS THE ASSOCIATION OF ITS RECEPTOR WITH A POSSIBLE SIGNAL TRANSDUCER, GP130.' * page 575, right column, line 8 - page 576, left column, line 10 * --- -/--	3	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K C07K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 07 JUNE 1993	Examiner RYCKEBOSCH A.O.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	



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Application Number

EP 92 11 7953

Page 2

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA. vol. 85, November 1988, WASHINGTON US pages 8037 - 8041 L. CHEN ET AL. 'GROWTH INHIBITION OF HUMAN BREAST CARCINOMA AND LEUKEMIA / LYMPHOMA CELL LINES BY RECOMBINANT INTERFERON-BETA-2.' * page 8040, left column, line 6 - line 10; table 2 * * page 8040, right column, line 16 - line 19 * * page 8040, right column, line 46 - line 50 *	1-4	
A	--- CHEMICAL ABSTRACTS, vol. 110, no. 25, 19 June 1989, Columbus, Ohio, US; abstract no. 229858y, G.J. FREEMAN ET AL. 'INTERLEUKIN 6 GENE EXPRESSION IN NORMAL AND NEOPLASTIC B CELLS.' page 486 ; * abstract * & J. CLIN. INVEST. vol. 83, no. 5, 1989, pages 1512 - 1518 -----	1-4	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
The present search report has been drawn up for all claims			
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